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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,119	BACUS, SARAH S.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Sections of Title 35, U.S. code not found in this Office action can be found in a previous action.

Claims 6 has been amended. Claims 1-6 are pending and under consideration under the limitation of the species of "apoptosis".

The rejection of claims 1, 2, 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) in view of the abstract of Bacus et al (Breast Cancer research and Treatment, 1999, vol. 57, page 55), Warri et al (Journal of the National cancer Institute, 1993, vol. 85, pp. 1412-1418), the abstract of Wu (Cancer Research, 1996, Vol. 16, pp. 2233-2239), the abstract of Fornier et al (Oncology, 1999, vol. 13, page 647-658) and the abstract of Lebwhol et al (Annals of Oncology, 1999, 10 suppl. 6, pp. 139-146) is maintained for reasons of record.

Claim 1 is drawn to a method for determining a response to administration of a chemotherapeutic or chemopreventative agent comprising collecting a first tissue or cell sample from an individual before exposing the individual to the chemotherapeutic or chemopreventative agent; collecting a second tissue or cell sample from the individual after exposing the individual to the chemotherapeutic or chemopreventative agent; immunohistochemically staining the first and the second tissue or cell samples using a detectably labeled antibody directed against a biological marker associated with apoptosis; measuring the optical density of the stained cells of step (c) wherein the stained cells are illuminated with light having a wavelength absorbed by the stain; determining whether expression of the biological marker associated with apoptosis was increased following exposure to the chemotherapeutic or chemopreventative agent. Claim 2 embodies the method of claim 1 wherein the detectable label is a chromogen or fluoraphore. Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is preformed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is preformed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells.

Bacus ('477) teaches a method for determining the effectiveness of a therapeutic agent in the treatment of cancer by measurement the ability of the therapeutic agent to induce terminal differentiation wherein malignant cells of the cancer over express an oncogene product comprising obtaining from a human having cancer a biopsy comprising viable malignant cells; dividing said biopsy into a first and a second portion; treating the first portion with a compound having specific binding affinity for said oncogene product; maintaining said first and second portions in physiologically acceptable medium for an amount of time sufficient to induce maturation in the viable malignant cells of the first portion; and comparing the percentage of cells in the first portion which exhibit markers of terminal differentiation with the percentage of cells in the second portion which exhibit markers of terminal differentiation, wherein the effectiveness of treatment correlated with the degree of terminal cell differentiation, or alternatively comparing the amount of oncogene product in said first portion with the amount of a oncogene product in said second portion (claims 1 and 10). Bacus teaches that cell proliferation is yet another measure of the extent of terminal cell differentiation, and that a stabilization and reduction of cell populations as compared to untreated control cells indicates substantial terminal differentiation (column 11, lines 53-61). Bacus teaches that induction of a translocation of the Her-2/neu receptor from the cell surface to the cytoplasm or perinuclear region of the cell induce a terminally differentiated phenotype in the tissue or cell sample is indicative of terminal differentiation and that this induction can be expedited by means of binding by antibodies (claims 4-6 and 11-17 and column 5, lines 1-38). Bacus teaches that normal cells are devoid of Her-2/neu on the surface membrane (column 4, lines 62-68). Bacus teaches the anti-Her-2/neu antibody conjugated to a fluorescent dye and indirect methods of antibody detection such as the use of peroxidase-anti-peroxidase staining or alkaline phosphatase staining, thus fulfilling the specific embodiment of claim 2. Bacus teaches that membrane bound Her-2/neu may be quantified by digitized image analysis in conjunction with fixation and staining procedures (column 11, lines 6-25). Bacus teaches that cell sample can be stained with an anti-Her-2 antibody and an additional DNA stain and that digitization of two filtered images of the single sample, one for each specific stain allows for the summation of the optical density value for the DNA stain and the optical density value for the Her-2/neu stain (column 10, lines 20-65), thus fulfilling the specific embodiments of claim 6. Bacus does not specifically teach the

binding and internalization of the Her-2/neu receptor with the induction of apoptosis in the tissue or cell sample, however, Bacus includes the stabilization and reduction of a cell population as part of the definition of terminal differentiation (column 11, lines 53-61).

Warri et al teach that methods for treating breast cancer should target the induction of apoptosis to breast cancer cells (abstract, last sentence).

The abstract of Wu teaches that apoptosis is a valuable marker for response in patients having primary or adjuvant chemotherapy fro breast cancer.

The abstract of Fornier et al teaches that clinical studies are underway in the treatment of breast cancer by the combined administration of Herceptin and Taxol. The abstract identifies Herceptin as a humanized antibody directed to the Her-2/neu protein.

The abstract of Lebwohl et al teaches that recent result indicate that the combined administration of Herceptin and doxorubicin result in a higher response rate and prolongs the time to disease progression when compared to chemotherapy alone.

Bacus et al teach that Taxol and doxorubicin affect apoptotic signaling in breast cancer cells by different mechanisms, namely, Taxol activated the p38 Map kinase cascade and doxorubicin activated the p38 jun kinase pathway. Bacus et al teach that inhibition of PI-3 resulted in the inhibition of doxorubicin induced cell cycle arrest. Bacus et al teach that Herceptin inhibits Pi-3 kinase. Bacus et al conclude that over expression of Her-2/neu or Her-3 in breast cancer patients will affect a patients response to chemotherapeutic reagents.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to evaluate a patients response to chemotherapy comprising the administration of Taxol and Herceptin or the administration of deoxyrubicin and Herceptin by means of obtaining a sample of cells or tissues from said patient before the chemotherapy and obtaining a second sample of cells or tissues from said patient after chemotherapy and quantitating the presence of Her-2/neu on the surface of said cells by means of an antibody labeled with a fluoraphore or a chromogen and quantitating the total number of cells by staining DNA, and subjecting the labeled cells to image analysis wherein the image analysis is performed by splitting a signal comprising the optical density of the stained biological sample into at least two signals that are processed using optical filters having different absorption and transmittance properties so that a signal from the labeled antibody can be separated from a signal from the

labeled DNA, so that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of the combined therapy in the induction of apoptosis in breast cancer cells in patients having undergone therapy. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Lebwhol and the abstract of Fornier et al on recent clinical trials using combinations of Herceptin with Taxol and doxorubicin, the teachings of Bacus et al which calls into question the interaction with Herceptin on the apoptotic pathways utilized by doxorubicin and Taxol; the teachings of Warri et al on the targeting of apoptosis to breast cancer cells as a therapeutic approach for treating breast cancer, the teachings of the abstract of Wu on the correlation between the induction of apoptosis and response to chemotherapy for breast cancer, and the teachings of Bacus ('477) on the targeting of stabilization and a reduction of a cell population in a method of treating breast cancer. One of skill in the art would know that the induction of apoptosis in breast cancer cells as a result of chemotherapy would result in a stabilization and reduction of a cell population which would fall under the definition of "terminal differentiation" set forth in Bacus ('477, column 11, lines 53-61).

Applicant argues that none of the references alone or in combination teach or suggest the instant method. applicant argues that Bacus I teaches the prognostication of the effectiveness of a therapeutic agent to induce terminal differentiation comprising using a single biopsy sample divided into two portions wherein one portion is exposed to the potential therapeutic agent and the other portion is not exposed the potential therapeutic agent. Applicant maintains that this is differs from the instant invention which requires obtaining a tumor cell sample form an individual before treatment and comparing it with a tumor cell sample after exposure of the individual to a therapeutic agent. this has been considered but not found persuasive. The difference cited by the applicant is one of in vitro versus in vivo exposure of tumor cells to a therapeutic agent, wherein Bacus teaches the in vitro method and the instant method is drawn to the in vivo method. One of skill in the art would always be motivate to extend in vitro methods of treating tumor cells to in vivo methods of treating patients with tumors as long as there was reasonable expectation of success. Thus, although Bacus teaches only a single biopsy sample, said sample is divided into two portions and one is exposed to a therapeutic agent and the other is

maintained as a control, the method of Bacus is analogous to the instant method wherein the first sample is the control because the individual with the tumor has not yet been exposed to the therapeutic agent and the second sample is after exposure to the therapeutic agent corresponding to a sample obtained from an individual after exposure to the agent in vivo. There is a direct correspondence with the method of Bacus.

Applicant argues that the deficiencies of Bacus are not "overcome" by the other sited art. however, the other cited art was to establish a motivation for testing an individual after exposure to combinations of agents, some of which, such as herceptin and doxorubicin, and as such appear contraindicated in in vitro studies. Thus, one of skill in the art would be motivated to verify whether combinations of chemotherapeutic drugs are actually effective in vivo by assessing the effect on tumor cells after exposure to the agents in vivo.

Applicant argues that Warri provides only a suggestion that the induction of apoptosis provides a "potential" new therapeutic approach for treating cancer. This has been considered but not found persuasive. one of skill in the art need only recognize that the induction of apoptosis in breast cancer would provide a reasonable expectation of success. Further, it is noted that the induction of apoptosis in breast cancer cells is synonymous with the killing of said breast cancer cells because one of skill in the at would known that apoptosis is a form of cell death. Applicant again points out that Warri fails to suggest the collection of a first and second sample. However, the collection of a first sample before exposure to a therapeutic agent and a collection of a second sample after exposure of a therapeutic agent is rendered obvious by Bacus who teaches exposure of a portion of a collected sample to a therapeutic agent as compared to a portion of the collected sample which is maintained as a control sample and not exposed to the therapeutic agent. Applicant argues that Warri does not teach the measurement of the optical density of the cells after immunohisotochemically staining said cells with a detectably labeled antibody directed against a biological; marker. this has been considered but not found persuasive as these claim limitations are taught by Bacus in reference to the sample exposed in vitro versus the sample maintained as a control (especially column 10, lines 20-65 and column 11, lines 6-25).

Applicant argues that reliance on Wu is misplaced as Wu teaches that apoptosis "may" have predictive value for the response to anti-cancer treatment. this has been considered but not

found persuasive. Wu et al state that "Mammary epithelial homeostasis is dependent not only on the rate of cell proliferation, but also on apoptosis, a genetically programmed process of autonomous cells death" and that "Overall, the evidence suggest that the progressive inhibition of apoptosis and induction of angiogenesis may contribute to tumor initiation" and that the apoptosis rate may have predictive value for the response to anti-cancer treatment. thus, Wu et al is summarizing what was recognized in the art that a decreasing rates of apoptosis contributed to tumor growth. Thus, one of skill in the art would recognize that an agent which increases the apoptosis rate of breast cancer cells would be therapeutic for the treatment of breast cancer. One of skill in the art need only to recognize a reasonable expectation of success in order to combine the teachings of Wu and Warri et al with the teaching of Bacus. Applicant argues that Wu does not teach or suggest that the actual response to a chemotherapeutic agent is can be determined by collecting a first and second sample. this has been considered but not found persuasive. The "first" and "second" sample correspond to the control and treated sample as set forth in Bacus, the office action relied on the teachings of Wu and Warri to establish that it was important to determine the degree of apoptosis induced by the therapeutic agent in vivo. The prior office action never relied on Warri or Wu to establish the taking of a first and a second sample as it as already noted that all these limitations were taught by Bacus. Applicant argues that Wu does not teach that that a response to a chemotherapeutic agent is determined immunohisochemically measuring the optical density of the cell. However, this limitation was taught by Bacus. Applicant argues that Wu does not teach a biological marker associated with senescence, apoptosis or terminal differentiation. This has been considered but not found persuasive. Firstly, the elected species is apoptosis, and accordingly, this is the only species that will be addressed. Secondly, Wu was not relied upon for those teachings, Wu was relied upon for motivation to look at apoptosis as an end-point to chemotherapy.

Applicant criticizes the reliance on Fornier et al stating arguments such as "does not teach method for identifying treatment efficacy by assaying markers of senesces, apoptosis or terminal differentiation". Once again, the elected species is "apoptosis". Applicant argues that somehow Fornier teaches against the instant invention because Herceptin as a therapeutic agent does not correspond to a detectably labeled antibody that could be used in immunohistochemistry. It is

noted that Herceptin is being relied upon as the antibody being used for the Her-2/neu stain, but as a therapeutic agent in combination with taxol, or in combination with doxorubicin.

Applicant argues that Lebwhol does not teach a method for determining a response of administration to an individual receiving such combination therapies, and that Lebwhol does not teach or suggest the presently clamed method of collecting a first and a second sample, corresponding to a tumor sample before and after the administration of a potential therapeutic agent or combination of agents. This has been considered but not found persuasive because Bacus teaches the limitation of evaluating a tumor cell after contacting with a chemotherapeutic agent in vivo in comparison with a portion of the tumor sample which was maintained as a control and not contacted to the therapeutic agent. Applicant argues that Lebwhol does not teach that that a response to a chemotherapeutic agent is determined immunohistochemically measuring the optical density of the cell. However, this limitation was taught by Bacus.

Applicant argues that Bacus II does not teach a method of determining a response of administration to an individual receiving taxol, doxorubicin and/or Herceptin, much less any other chemotherapeutic agent. this has been considered but not found persuasive. Determining the response of a tumor cell after contact with a therapeutic agent is taught by Bacus I. Bacus II is relied upon for teachings regarding the overexpression of the Her-2/neu versus Her3 in breast cancer patients and the associated difference in response to chemotherapeutic agents as a function of expression of Her-2/neu or Her3. One of skill in the art would conclude that not all breast cancer patients will respond in the same way to the same agents based on differential expression of these ErbB receptors. Thus, there would be ample motivation to assay tumor cells taken from a patient before exposure to a chemotherapeutic agent and after exposure to a chemotherapeutic agent.

Applicant argues that the mere fact that the individual references can be combined does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. This has been considered but not found persuasive. It is noted that the prior art recognizes that individual variations can influences a patients response to a therapeutic agent directed against breast cancer (Bacus II). Thus, one of skill in the art would be motivated to use the method taught by Bacus I to assay if a therapeutic response was attained in an individual. Applicant argues that the Federal Circuit has recently re-emphasized the importance of the

motivation to combine. This has been considered but not found persuasive. First on reviewing the cited In re Mills, it is noted that the fact pattern is not the same as the fact pattern regarding the rejection of the instant claims. The court stated that

"The essence of Mills' invention is the machine's ability to aerate a cementitious composition by driving the output pump at a capacity greater than the feed rate, thereby drawing air into the composition. This aeration produces a composition with substantially lower density than standard cementitious composition mixing ingredients". The court concluded that ."After reviewing the record, the arguments in the briefs, and the Mathis reference, we conclude that Mathis would not have rendered the claimed invention obvious. The closest Mathis comes to suggesting Mills' claimed apparatus is at column 3, lines 42-47, which states the rate at which the inlet 2b receives a solid constituent depends on the speed of the feed screw 4. Such speed can be regulated by a prime mover 6 which includes a variable-speedtransmission. This brief reference contains no suggestion of "pump means and the feed means providing a pumping capacity of the pump means greater than the feed rate of ingredients to the mixing chamber provided by the feed means, such that in operation air is drawn into the mixing chamber, and air entrained in the mixed ingredients," as provided for in Mills' claim 6. While Mathis' apparatus may be capable of being modified to run the way Mills' apparatus is claimed, there must be a suggestion or motivation in the reference to do so. See In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). We see no such suggestion. The apparatus claimed by Mills is different from that of Mathis, since the fact that motor 6 of Mathis (the feed means) can be run at a variable speed does not require that motor 20 (connected to the pump) be run at a lesser speed "such that in operation air is drawn into the mixing chamber and air entrained in the mixed ingredients.".

In the In re Mills case, only one reference was used by the examiner without another reference or reasoning which would provide motivation to combine two references. In the instant case, Bacus I provides the main teachings but in regard to the contacting of tumor cells with therapeutic agents in vitro and measuring markers of terminal differentiation as a means of inducing stabilization and reduction of a tumor cell population, and other references such as Bacus II provide motivation whereby one of skill in the art would be motivated to use tumor samples obtained from patients to measure markers of apoptosis as therapeutic goal to the elimination of tumor cells from a patient. There is ample motivation to one of skill in the art to assess if a therapeutic agent was really working in an individual, given that Bacus II teaches that the expression of ErbB receptors have different signaling pathways and can effect individual responses to therapeutic agents.

Applicant argues that motivation cannot be solely based on common knowledge or common sense as determined in re Lee 61 USPQ.2d 1430 (Fed Cir 2002). This has been considered but not found persuasive, On page 1433, the court stated that

The need for specificity pervades this authority. See, e.g., In re Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459(Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination [emphasis added]" and on page 1434 that "In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783(Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references" [emphasis added]).

The examiner contends that in this case it is clear from the record that an individuals response to chemotherapy varies with the particular ErbB receptors being expressed by the breast tumors, and the motivation to assay the therapeutic effect by means of Bacus I would be obvious in order to assess if tumor cells were killed within the patient. Knowledge generally available to one of skill in the art is that the killing of tumor cells within a patient is desirable and that methods for assaying changes in tumor cells exposed to agents in vitro can be used to assay for changes in tumor cells in vivo. One of skill in the art would be motivated to use the assays of Bacus I with samples obtained from actual clinical samples both before and after treatment with a therapeutic agent or agents in order to assess a patients response to the therapeutic agent..
In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The rejection of claims 1-3, 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) in view of the abstract of Bacus et al (Breast Cancer Research and Treatment, 1999, vol. 57, page 55), Warri et al (Journal of the National cancer Institute, 1993, vol. 85, pp. 1412-1418), the abstract of Wu (Cancer Research, 1996, Vol. 16, pp. 2233-2239), the abstract of Fornier et al (Oncology, 1999, vol. 13, page 647-658) and the abstract of Lebwhol et al (Annals of Oncology, 1999, 10 suppl. 6, pp. 139-146) as applied to claims 1, 2, 5 and 6 above, and further in view of Caffo et al (Clinical Cancer research, 1996, vol. 2, pp. 1591-1599), the abstract of el-Deiry et al (Cancer Research, 1995, Vol. 55, pp. 2910-2919) the abstract of Thor et al (Journal of the National cancer Institute, 1992, Vol. 84, pp. 845-855) and the abstract of Shetty et al (Leukemia Research, 1996, vol. 20, pp. 11-12) is maintained for reason of record.

The specific embodiments of claims 1, 2, 5 and 6 and the teachings of the combination of references that render obvious said embodiments are set forth above. Warri further teach that induction of apoptosis in human breast cancer cells results in an elevated level of mRNA for TGF-beta.

Claim 3 is drawn in part to the method of claim 1 wherein the biological marker is p21 or TGF-beta.

Neither Bacus ('477) the abstract of Bacus et al, Warri et al, the abstract of Fornier et al nor the abstract of Lebwhol teach p21 as the biological marker protein. Warri et al teach that mRNA for TGF-beta is a biological marker for apoptosis (the bottom of page 1416 to the top of page 1417, "The apoptotic changes observed in this study were connected with an elevation in the levels of both TRMP-2 and TGF-beta mRNAs"). It is reasonable to conclude that TGF-b protein was elevated as a result of the elevation of TGF-beta mRNA.

Caffo et al teach that chemotherapy or radiotherapy induces DNA damage which activates P53 function, which in turn blocks the cell cycle to allow DNA repair or apoptosis, but that this activation depends on the functional status of p53. Caffo et al teach that the way to confirm the functional status of p53 is to measure downstream effector functions such as the activation of p21 (page 1596, first paragraph under the heading of "Discussion"). Caffo et al teach that the phenotype of p21 negative/ p53 positive is indicative of a phenotype which cannot activate the apoptotic cascade in response to DNA damaging drugs (page 1591, second column,

lines 1-6). Caffo et al teach that in breast cancer patients treated with systemic adjuvant therapy, p21 positive/ p53 positive tumors were associated with long disease free survival and long overall survival, but that patients having p21 negative/ p53 positive tumors had short disease free survival and short overall survival (page 1591, first column lines 17-21 and table 3, under the heading "Patients treated with any adjuvant therapy"). . Caffo et al conclude that the p21/p53 phenotype may be of clinical relevance concerning the response to chemotherapy/hormone therapy and that the p21 negative/ p53 positive phenotype could corresponds to a situation where p53 is expressed but lacks transcriptional activity because of mutational or functional inactivation and that this phenotype reflexes the complete abrogation of p53 function; Caffo et al further teach that in p21 negative/ p53 positive cases the tumor cells have an impaired G1 checkpoint and may not be able to activate the apoptotic cascade in response to DNA damaging chemotherapy and thus can be more prone to treatment failure by conventional therapy (page 1599, first full paragraph).

The abstract of el-Deiry et al teaches that antibodies to human p21 can be used in immunohistochemical analysis to monitor the effects of radiation induced damage.

The abstract of Thor et al teaches that antibodies to human p53 can be used in immunohistochemical analysis to detect p53 in archival samples of breast carcinomas.

The abstract of Shetty et al teaches that antibodies to human TGF-beta can be used in immunohistochemical analysis to monitor the expression of TGF-beta in cells of myelodysplastic syndromes.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to include the antibodies which bind to p21, p53 and TGF-beta to the method rendered obvious by the combination of Bacus ('477) the abstract of Bacus et al, Warri et al, the abstract of Fornier et al and the abstract of Lebwhol. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Warri et al on the up regulation of expression of TGF-beta after treatment with an anti-estrogen compound which causes apoptosis in breast cancer cells; the teachings of Caffo et al on the importance of the p21 and p53 phenotypes of breast tumors in the response to chemotherapy, and the teachings of the abstracts of el-Deiry et al and Thor et al and Shetty et al who teach that antibodies to p21, p53 and TGF-beta are available and useful for immunohistochemistry.

Furthermore, one of skill in the art would conclude that if the remaining tumor cells were p21 negative/ p53 positive, chemotherapy should be stopped.

Applicant argues that the teachings of Caffo do not remedy the deficiency of the combination of Bacus I, Warri, Wu , Fornier, Lebwhol and Bacus II. this has been considered but not found persuasive because the combination of Bacus I, Warri, Wu , Fornier, Lebwhol and Bacus II render obvious claims 1, 2, 5 and 6 for the reasons set forth above.

Applicant argues that the teachings of Warri et al regarding the nexus between TGF-beta mRNA expression and TGF-beta protein expression as faulty but does not provide a reason to refute this. Applicant has not provided any indication that an increase in the level of mRNA encoding TGF beta would not be expected to produce a concomitant increase in the level of TGF-beta protein. Applicant concludes that one of skill in the art based on the teaching of Lebwhol would not conclude that TGF-beta protein is a marker for apoptosis because only a slight affect on TGF-beta. this has been considered but not found persuasive, as Warri et al concludes that "The apoptosis changes observed in this study were connected with an elevation in the levels of both TRMP-2 and TGF-beta mRNAs" and further, the claims do not contain any specific limitations regarding the level of expression of the apoptosis markers, therefore, arguments regarding "a slight affect" are moot.

Applicant argues that Caffo et al teach that p21 may provide prognostic information and that this somehow teaches against using it as a marker in the instant invention. This has been considered but not found persuasive. Applicant is ignoring the teachings of Caffo et al which state that in p21 negative/ p53 positive cases the tumor cells have an impaired G1 checkpoint and may not be able to activate the apoptotic cascade in response to DNA damaging chemotherapy and thus can be more prone to treatment failure by conventional therapy (page 1599, first full paragraph). One of skill in the art would be motivated to assay for both p21 and p53 in patients undergoing treatment with an anti-tumor therapeutic agent targeted to induce apoptosis in order to determine if in fact said patients has tumor cells which were resistant to the treatment. One of skill in the art would be motivated to determine if said patient were resistant to the treatment in order that said treatment can be stopped , and another treatment can be selected.

Applicant argues that el-Deiry , Thor and Shetty do not teach that the disclosed antibodies could be used for determining a response to the administration of a therapeutic agent

and that this somehow teaches against the use of said antibodies in the method of Bacus I. This has been considered but not found persuasive. The reference wee relied upon to demonstrate that antibodies directed to p21 and p53 can bind to p21 and p53 in tissue samples One of skill in the art would conclude that said antibodies would show the same selectivity to p21, p53 and TGF-beta in the tumor cells obtained from a patient both before and after treatment with a therapeutic agent. The nature of antibodies is that they bind to specific epitopes. The references demonstrate that antibodies are availed which bind to epitopes which are accessible in immunohistochemistry. It would be logical to conclude that if p21, p53 or TGF-beta were present in the tumor cells of the instant invention, the antibodies of el-Deiry, Thor and Shetty would bind to said epitopes of the tumor cells.

Applicant maintains on page 16 that the teachings of Caffo are limited to whether p21 could be used a s predictive marker, the reference does nothing to add to the fatally defective combination of Bacus I, Bacus II, Warri, Wu, Fornier and Lebwhol references and by itself does not teach r suggest methods of determining or monitoring the response to chemotherapy. this has been considered but not found persuasive. firstly the combination of Bacus I, II, Warri, Wu, Fornier and Lebwhol render obvious claims 1, 2, 5 and 6 for the reasons set forth above. applicant is ignoring the pertinent teachings of Caffo et al which were set out in the Office action, specifically that in p21 negative/ p53 positive cases the tumor cells have an impaired G1 checkpoint and may not be able to activate the apoptotic cascade in response to DNA damaging chemotherapy and thus can be more prone to treatment failure by conventional therapy (page 1599, first full paragraph). this has been presented as motivation for monitoring p21 after the administration of chemotherapy. One of skill in the art would be motivated to measure p21 and p53 as a response to chemotherapy which targets the induction of apoptosis in cancer cells i order to ascertain if said chemotherapy is resulting in an efficacious response. In the case where an individual exhibits p21 negative/p53 positive tumor cells after a course of therapy designed to induce apoptosis i tumor cells, said therapy should be curtailed because it will be ineffective against the remaining tumor cells. One of skill in the art would be motivated to terminate and inappropriate therapy in a patient in order that a different more effective therapy can be administered to said patient.

Applicant argues on the bottom of page 16, that because el-diery, Thor and Shetty merely describe specific antibodies to biological markers associated with senescence, apoptosis or terminal differentiation, they do not contemplate a method for determining or monitoring a response using these specific antibodies, much less a method of the present inventi0on of determining a response by immunohistochemical staining two samples. this has been considered but not found persuasive. Bacus I teaches the immunohistochemical stating of a tumor sample, both before and after exposure to a agent targeting the terminal differentiation of said tumor cells The references demonstrate that antibodies are available which bind to epitopes which are accessible in immunohistochemistry. It would be logical to conclude that if p21, p53 or TGF-beta were present in the tumor cells of the instant invention, the antibodies of el-Deiry, Thor and Shetty would bind to said epitopes of the tumor cells.

The rejection of claims 1-3, 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) in view of the abstract of Bacus et al (Breast Cancer research and Treatment, 1999, vol. 57, page 55), Warri et al (Journal of the National cancer Institute, 1993, vol. 85, pp. 1412-1418), the abstract of Wu (Cancer Research, 1996, Vol. 16, pp. 2233-2239), the abstract of Fornier et al (Oncology, 1999, vol. 13, page 647-658) and the abstract of Lebwhol et al (Annals of Oncology, 1999, 10 suppl. 6, pp. 139-146) as applied to claims 1, 2, 5 and 6 above, and further in view of Hochhauser (Anti-Cancer Drugs, 1997, vol. 8, pp. 903-910), the abstract of Ohtani et al (Cancer, 1999, vol. 85, pp. 1711-1718) and the abstract of Emig et al (British Journal of Cancer, 1998, Vol. 78, pp. 1661-1668) is maintained for reasons of record.

The specific embodiments of claims 1, 2, 5 and 6 and the teachings of the combination of references that render obvious said embodiments are set forth above.

Claim 3 is drawn in part to the method of claim 1 wherein the biological marker is p27 or p16.

Neither Bacus (U.S. 5,288,477), the abstract of Bacus et al, Warri et al, the abstract of Fornier et al nor the abstract of Lebwhol teach p27 or p16 as the biological marker protein.

Hochhauser teaches that alterations in cell cycle genes can sensitize cells to apoptosis following treatment with chemotherapeutic agents (page 908, first sentence under the heading "Conclusion"). Hochhauser teaches that induction of p16 expression results in reversible cell

cycle arrest which renders cells resistant to a variety of chemotherapeutic agents including methotrexate, cisplatin and vincristine (page 906, second column, lines 7-13). Hochhauser also teaches that expression of p27 in tumors is related to acquired drug resistance to chemotherapeutic agents (page 907, under the heading "p27 and chemosensitivity").

The abstract of Ohtani et al teaches that antibodies to human p27 can be used in immunohistochemical analysis to monitor the expression of p27 in gastric cancer cells and that decreased levels of p27 are indicative of decreased rates of apoptosis in said cells.

The abstract of Emig et al teaches antibodies to human p16 can be used in immunohistochemical analysis to monitor the expression of p16 in breast cancer cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to include antibodies to p16 and antibodies to p27 in the method rendered obvious by the combination of Bacus ('447), the abstract of Bacus et al, Warri et al, the abstract of Wu, the abstract of Fornier et al and the abstract of Lebwhol et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Hochhauser on the inverse relationship between the expression of p27 and p16 and the induction of apoptosis by chemotherapeutic agents, and the teachings of the abstracts of Ohtani et al and Emig et al on the availability of antibodies to human p16 and p27 and usefulness of said antibodies for immunohistochemistry.

Applicant argues that the Hochhauserauser reference merely reports gene expression changes that accompany apoptosis, but that Hochhauserauser does not teach or suggest any methods that utilize the information regarding p16 or p27 much less the methods of the present invention. applicant is ignoring the teachings of Hochhauserauser set forth and relied upon in the previous office action that Hochhauser teaches that alterations in cell cycle genes can sensitize cells to apoptosis following treatment with chemotherapeutic agents (page 908, first sentence under the heading "Conclusion"). Hochhauser teaches that induction of p16 expression results in reversible cell cycle arrest which renders cells resistant to a variety of chemotherapeutic agents including methotrexate, cisplatin and vincristine (page 906, second column, lines 7-13). Hochhauser also teaches that expression of p27 in tumors is related to acquired drug resistance to chemotherapeutic agents (page 907, under the heading "p27 and

chemosensitivity"). The teaching of Hochhauser et al provide ample motivation to monitor the expression of both p16 and p27 during chemotherapy.

Applicant argues that Ohtani somehow teaches against the instant invention because Ohtani correlated the decreased expression of p27 with predicting a poor prognosis for patients with late-stage gastric carcinoma. this is not persuasive as there is no claim limitation specifying that the detection of p27 must only be for increases in expression rather than decreased expression.

Applicant argues that Emig does not tech the instant invention, however, Emig was relied upon for the identify of antibodies which bind to human p16 which can be used to monitor expression of p16 in breast carcinoma cells.

The essential disagreement with the instant 103 rejections is that applicant maintains that Bacus I does not teach most of the limitation of the instant claims because the Bacus I assay is done on a tumor sample before and after exposure to a chemotherapeutic agent in vitro and the instant claims are drawn to assaying a tumor sample taken from an individual both before and after exposure to a therapeutic agent in vivo. The examiner contends that it would be obvious to use the method of Bacus I on a clinical sample taken from an individual both before and after treatment in order to assay for markers of terminal differentiation and apoptosis. The applicants maintains that it is not obvious in light of the fact that one of skill in the art is motivated to treat tumors in actual patients and monitor the effects of said treatment.

The rejection of claims 1, 2, 4 and 5 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Meyn et al (Anticancer Drugs, 1995, vol. 6, pp. 443-450) in view of Riss (U.S. 6,350,452) and Bjorklund et al (WO 99/16789) and Schlossman et al (U.S. 5,935,801) and Desjardins (U.S. 5,972,622) is maintained for reasons of record..

The abstract of Meyn teaches seven different murine tumors comprising a mammary adenocarcinoma, an ovarian carcinoma, a lymphoma, three sarcomas, and a squamous cell carcinomas were examined 8 and 24 hours after treatment in vivo with cisplatin or cyclophosphamide and that the mammary adenocarcinoma, ovarian carcinoma, and lymphoma exhibited significant apoptosis in response to cisplatin or cyclophosphamide. The abstract further teaches that the mammary carcinoma and the ovarian adenocarcinoma also underwent

apoptosis in response to adriamycin, 5-fluorurcil, Ara-C, etoposide, campothecin, and fludarabine. Meyn et al conclude that apoptosis is a feature of tumor response to chemotherapy in vivo and notes the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents.

Riss teaches antibodies that recognize an epitope of the PARP protein formed by cleavage of said protein by caspases (column 3, lines 26-51). Riss teaches a method for detecting apoptosis in a cell or a group of cells including tissue samples and biopsy samples (column 4, lines 1-20) comprising detecting the neo-epitope bound by the anti-PARP protein by means of ELISA, immunohistochemistry , immunocytochemistry and flow cytometry (column 4, lines 21-46). Accordingly Riss contemplates detectably labeled antibody with a fluoraphore or chromogen (column 4, lines 47-64, and column 14, line 45 to column 16, line 40), thus fulfilling the specific embodiments of claim 2, drawn to the labeling of the antibody with a fluoraphore or chromogen, claim 4, drawn to ELISA assay and claim 5 drawn to image analysis, which would be satisfied by flow cytometry..

Bjorklund et al teach a method for detecting early apoptotic changes in epithelial cells comprising contacting said cells with the M30 antibody which binds to an epitope of keratin 18 that is exposed after cleavage by caspases (page 2, lines 1-9 and 29-32). Bjorklund et al teach that the preferred embodiments of the method include determination of the rate of apoptosis, which is useful in the diagnosis of diseases such as cancer and for monitoring the effect of therapy (page 10, lines 5-8). Bjorklund et al teach that the antibody can be used in different immunoassays labeled in accordance with the actual assay used (page 10, lines 25-27) and contemplates enzymes and fluorescent markers (page 8, lines 30-31). Bjorklund et al teach the immunoassay which may be used in the method include ELISA and dissociation enhancement time-resolved fluoroimmunoassay, thus fulfilling the specific embodiments of claims 2, 4 and 5 Bjorklund et al teach that the M30 antibody staining is applicable to fresh, formalin fixed paraffin embedded tissue sections from biopsy (page 17, lines 30-34).

Schlossman et al teach an antibody which binds to an epitope localized on the membrane of mitochondria, 7A6, wherein said epitope is present only in cells undergoing apoptosis (column 1, lines 5-9, column 5, lines 38-65). Schlossman et al teach that said antibody is labeled with a fluoraphore or chromogen and used in flow cytometry or ELISA assays to detect

apoptotic cells (column 7, line 47 to column 8, line 44, column 9, line 59 to column 10, line 13) thus fulfilling the specific limitations of claims 2, 4 and 5. Schlossman et al teach that said antibody can be used in vitro in assays which compare the level of apoptotic cells in treated and untreated tumor cells (column 12, lines 39-43) and to monitor the efficacy of therapeutic regiments (column 2, lines 41-47).

Desjardins teaches the need for markers of apoptosis in order to determine whether apoptosis has been induced in tumor cells by cancer chemotherapy. Desjardins teaches that identification of said markers would be an improvement over the prior art which relies on direct measurements of tumor size in vivo (column 2, lines 54-63). Desjardins teaches anti-GP46 antibodies, which specifically target apoptotic cells (column 8, lines 7-15) which can be used to monitor the treatment of a disease (column 6, lines 15-17). Desjardins teaches the labeling of said antibodies with fluoraphores and chromagens (column 11, lines 3-18), and the detection of said labeled antibody in antibody-antigen complexes, by any procedure known in the art, such as ELISA and fluorescent immune assay, including single and double antibody techniques (column 11, lines 54-56). Further, any immunoassay known in the art would also include flow cytometry. Thus, Desjardins teach the specific embodiments of claims 2, 4 and 5.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use any of the antibodies taught by Riss, Bjorklund et al, Schlossman et al or Desjardins in a method of monitoring the efficacy of chemotherapy in an individual, wherein a sample of cells or tumor tissue was taken from said individual before and after the administration of a chemotherapeutic drug, and wherein the analysis was done by means of ELISA or image analysis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Meyn et al on apoptosis as a feature of tumor response to chemotherapy in vivo, and the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents; the teachings of Bjorklund et al on the use of the M30 antibody on monitoring the effect of therapy; the teachings of Schlossman et al on the use of the anti-7A6 antibody in monitor the efficacy of therapeutic regiments; and the teachings of Desjardins on the use of the anti-GP46 antibody in determining whether apoptosis has been induced in tumor cells by cancer chemotherapy. One of skill in the art would be motivated to substitute the assay based on antibody binding for the conventional assays of tumor

size measurement because Desjardins teaches that said conventional assays require at least a month of treatment before a detectable difference would be measured, whereas an immunoassay on cells or tissues taken from the individual before and 8 or 24 hours after chemotherapy would measure the percentage of apoptotic cells resulting from one treatment. Thus, it would be possible to determine a likelihood of a response to a particular chemotherapeutic agent after one treatment rather than a month of treatments.

Applicant argues that Meyn teaches that apoptosis may be a feature of tumor response to chemotherapy in vivo. applicant concludes that this somehow disqualifies the teaching of Meyn et al. firstly, one of skill in the art nee only a reasonable expectation of success in order to combine the references. Secondly Meyn et al teach mammary adenocarcinoma, ovarian carcinoma, and lymphoma exhibited significant apoptosis in response to cisplatin or cyclophosphamide. This is a fact not a speculation. Meyn notes the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents and this is ample motivation to monitor the degree of apoptosis in response to every individual patient being administered cytotoxic agents. One of skill in the art would want to be assured that an efficacious response were being attained by said in vivo treatment and in light of heterogeneous responses, there is strong motivation to monitor the individual response after a treatment.

Applicant argues that Riss only teaches the specific use of the antibodies which recognize the PARP protein. This is not persuasive because Riss teaches a method for detecting apoptosis in a cell or a group of cells including tissue samples and biopsy samples (column 4, lines 1-20) comprising detecting the neo-epitope bound by the anti-PARP protein.

Applicant argues that although Borklund teaches that the rate of apoptosis may be used in the diagnosis of disease with involvement of apoptosis, such as degenerative disease and cancer, and in the monitoring of therapy" but that Borklund does not teach what type of therapy should be monitored. applicant argues that Desjardins teaches that the anti-GP-46 antibody can be used in methods that require specific targeting of tumor cells and that said antibody can be used for the detection of apoptosis and to monitor the treatment of disease, but does not teach what type of therapy should be monitored. this is not persuasive. The instant claims encompass monitoring markers of terminal differentiation and apoptosis. They do not dictate what type of therapy is to be monitored. applicant is argue limitations that are not part of the claims.

The rejection of claims 1, 2 and 4-6 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Meyn et al (Anticancer Drugs, 1995, vol. 6, pp. 443-450) in view of Riss (U.S. 6,350,452) and Bjorklund et al (WO 99/16789) and Schlossman et al (U.S. 5,935,801) and Desjardins (U.S. 5,972,622) as applied to claims 1, 2, 4 and 5 above, and further in view of Bacus (U.S. 5,288,477) is maintained for reasons of record. The specific embodiments of the claims are recited above, and the prior art teachings which render obvious said embodiments. The combination of Meyn et al and Riss and Bjorklund et al and Schlossman et al and Desjardins do not specifically teach the embodiments recited in claim 6, drawn to the use of optical filters for the separation of the signals produced by a multiplicity of stains.

Bacus teaches that cell sample can be stained with an antibody and an additional DNA stain, and that digitization of two filtered images of the single sample, one for each specific stain allows for the summation of the optical density value for the DNA stain and the optical density value for the antibody stain (column 10, lines 20-65), thus teaching the specific embodiments of claim 6.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to include a DNA stain with the detectably labeled antibody and perform image analysis by splitting a signal comprising the optical density of the stained biological sample into a multiplicity of signals, comprising at least one signal for a DNA stain and one signal for an anti-apoptotic antibody stain which are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells in the biological sample. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Bacus on the inclusion of a DNA stain to determine the total number of cells in the sample (column 10, lines 20-65). One of skill in the art would know that the DNA stain would serve to quantify the total number of cells and thus the ratio of the antibody stain to the DNA stain would give the percentage of apoptotic cells in a sample.

Applicant argues on page 25 that the office does not set forth a reference to establish that the optical density value for the DNA stain would serve as a surrogate for the number of cells in the sample. the optical density value for the DNA stain as taught by Bacus I will be indicator of

the number of cells in the sample because every cell in the sample will have a nucleus which will stain with DNA, thus one of skill in the art will obtain a number of nuceli and know that this represents the number of cells. applicant has not provided an facts or reasoning why the number of cells staining with the DNA stain would not be the same as the total number of cells in the population. Applicant again argues impermissible hindsight. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant again argues against the Bacus I reference marinating that Bacus I does not teach most of the limitation of the instant claims because the Bacus I assay is done on a tumor sample before and after exposure to a chemotherapeutic agent in vitro and the instant claims are drawn to assaying a tumor sample taken from an individual both before and after exposure to a therapeutic agent in vivo. the examiner contends that it would be obvious to use the method of Bacus I on a clinical sample taken from an individual both before and after treatment in order to assay for markers of terminal differentiation and apoptosis. the applicants maintains that it is not obvious even in light of the fact that one of skill in the art is motivated to treat tumors in actual patients and monitor the effects of said treatment.

The rejection of claims 1, 2, 4 and 5 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Meyn et al (Anticancer Drugs, 1995, vol. 6, pp. 443-450) in view of Riss (U.S. 6,350,452) and Bjorklund et al (WO 99/16789) and Schlossman et al (U.S. 5,935,801) and Desjardins (U.S. 5,972,622) as applied to claims 1, 2, 4 and 5 above, and further in view of the abstract of Booth et al (Apoptosis, 1996, Vol. 1, pp. 191-200), the abstract of Shen et al (Cancer, 1998, Vol. 82, pp. 2373-2381), the abstract of Hiraishi et al, Glycobiology, 1993, Vol. 3, pp. 381-390), the abstract of Cutrona et al(Journal of Experimental Medicine, 1995, vol. 181, pp. 699-711), the abstract of Frankfurt et al (anticancer Research, 1996, Vol. 16, pp. 1979-1988) is maintained for reasons of record.

The abstract of Booth et al teaches that antibodies raised to the peptide DVVDADEYLIPQ were are a useful marker of apoptotic cell in the intestinal epithelium.

The abstract of Shen et al teaches that the Ki-67 antibody is indicative of apoptosis.

The abstract of Hiraishi et al teaches that antibodies which bind to Ley are indicative of apoptosis.

The abstract of Cutrona et al teaches that expression of CD10 and CD38 on the surface of lymphoma cells was indicative of said cells undergoing apoptosis.

The abstract of Frankfurt et al teaches that monoclonal antibodies which bind to single stranded DNA are indicative of apoptosis.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use any of the above antibodies in the method of detecting apoptosis as a result of chemotherapy as rendered obvious by the combination of Meyn et al, Riss, Bjorklund et al, Schlossman et al and Desjardins. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the abstracts of Booth et al, Shen et al, Hiraishi et al, Cutrona et al Frankfurt et al and Attallah et al all who all teach alternative antibodies which specifically bind to apoptotic markers.

Applicant argues that because the combination of Meyn et al, Riss, Bjorklund et al, Schlossman et al and Desjardins is defected the additional cited references do not remedy the deficiencies of the rejection. this is not persuasive. the combination of Meyn et al, Riss, Bjorklund et al, Schlossman et al and Desjardins is not defective for the reasons set forth above. the additional references were relied upon as identifying alternate antibodies which bind to apoptotic markers. again applicant argues no motivation to combine the references and impermissible hindsight. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Meyn notes the heterogeneity of apoptotic response between different tumor types and to different cytotoxic agents and this is ample motivation to monitor the degree of apoptosis in response to every individual patient being administered cytotoxic agents. one of skill in the art would want to be assured that an efficacious response were being attained by said in vivo treatment and in light of heterogeneous responses, there is strong motivation to monitor the individual response after a treatment.

The rejection of claims 1, 2 and 4 and 5 under 35 U.S.C. 103(a) as being unpatentable over the abstract of Meyn et al (Anticancer Drugs, 1995, vol. 6, pp. 443-450) in view of Riss (U.S. 6,350,452) and Bjorklund et al (WO 99/16789), Schlossman et al (U.S. 5,935,801) and Desjardins (U.S. 5,972,622) and Bacus (U.S. 5,288,477)) as applied to claims 1, 2 and 4-6 in section 10 above, and further in view of Pamukcu et al (U.S. 5,852,035), Smith-McCune et al (WO 99/24620) and the abstract of Attallah et al (Hepato-Gastroenterology, 1996, Vol. 43, pp. 1305-1312) is maintained for reasons of record. Claims 1, 2, 4 and 5 are drawn in part to methods for determining the response of administration of a chemopreventative agent to an individual. The combination of Meyn et al, Riss, Bjorklund et al, Schlossman et al and Desjardins render obvious the specific limitations of the claimed methods with respect to determining the response to a chemotherapeutic agent. Neither Meyn et al, Riss, Bjorklund et al, Schlossman et al nor Desjardins teach a method for determining the response to a chemopreventative agent.

Pamukcu et al teach a method for treating pre-malignant lesions including colonic polyps and cervical dysplasia by administering compounds which induce apoptosis in said neoplastic tissues (column 5, lines 13-32).

Smith-McCune et al teach a methods of screening for cervical dysplasia and cervical cancer comprising the measurement of apoptotic cells in cervical samples (page 3, lines 16-25, page 10, lines 24-26). Smith-McCune et al teach that the apoptotic rate is unregulated in dysplastic tissue (page 8, lines 19-20).

The abstract of Attallah et al teaches that antibodies which bind to CK1 can be used to quantify apoptotic epithelial cells in premalignant lesions of the gastric mucosa.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method rendered obvious by the combination of Meyn et al, Riss, Bjorklund et al, Schlossman et al and Desjardins in a method of determining a response to a chemopreventative agent, such as those compounds taught by Pamukcu et al, in an individual having pre-malignant lesions or dysplasia. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Pamuku et al on the induction of apoptosis in pre-malignant lesions as a target for therapy; and the teachings of Smith-McCune on the correlation between apoptotic rate and dysplasia and the teachings of the abstract of Attallah et al on the use of antibodies to quantify apoptosis in premalignant lesions.

Applicant argues that Pamuku and Smith-McCune and Attallah do not teach or even suggest a method of collecting both a first and a second sample from an individual both before and after exposing said individual to a chemotherapeutic agent and measuring the optical density of the cells after immunohistochemically staining them with a detectable labeled antibody associated with apoptosis. This is not persuasive as any antibody which is detectable labeled and reacted with an antigen on a tissue sample will fulfill the specific embodiment of claim 1 because the measurement of optical density of the stained cells wherein the stained cells are illuminated with light having a wavelength absorbed by the stain reads on the quantitation of any antibody binding wherein the quantitation is on the basis of a detectably labeled antibody.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
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02/23/04

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PRIMARY EXAMINER